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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,821	09/30/2005	Janus S. Larsen	2815-0327PUS1	3989

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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/551,821	LARSEN ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *September 30, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application is a national stage application of PCT/EP04/50427, filed April 2, 2004, which claims benefit of provisional application 60/461794, filed April 11, 2003, and claims priority to foreign application DK PA 2003 00557, filed April 10, 2003. Claims 1-11 are pending in this application and examined on the merits herein. Applicant's preliminary amendment submitted September 30, 2005 is acknowledged wherein claims 4-7 and 9-11 are amended and claim 12 is cancelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing anesthesia, pre-anesthesia muscle relaxation, does not reasonably provide enablement for a method of treating any disease, disorder, or condition responsive to modulation of the GABA receptor complex. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a

disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a therapeutic method. In order to be enabled, a therapeutic method must be directed to disorders that are known, either in the art or the specification, and which one skilled in the art would recognize as treatable.

The state of the prior art: There exist three subtypes of GABA receptors. Agonists of the GABA receptors are known in the art to be useful as anesthetics and sedatives. They are useful, for example, for the induction of anesthesia during surgery or for the treatment of epilepsy and insomnia. However, the full scope of all conceivable disorders responsive to GABA modulation is not known.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Biological systems are complex, particularly neurological systems, and the action of one particular receptor can induce a wide variety of effects and be implicated in many different diseases. Because of the ubiquity of GABA as a major inhibitory neurotransmitter and the multiple subtypes of GABA receptors, a wide variety of different conditions are expected to be "responsive to

modulation of the GABA receptor complex." Determining the full scope of these conditions would require a significant amount of unpredictable experimentation.

The Breadth of the claims: The claimed invention is very broad, encompassing methods of treating any disorder whatsoever that happens to respond in any way to modulation of the GABA receptor.

The amount of direction or guidance presented: Applicant discloses that the claimed compounds are agonists of the GABA receptor. It is suggested that these compounds could be useful as anesthetics.

The presence or absence of working examples: No working examples are provided for the treatment of any disorder.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable biological system such as the brain . See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention for the full scope of all possible GABA-responsive disorders, one skilled in the art would have to be in possession of the full scope of all possible disorders responsive to GABA modulation. Because of the complexity of the brain and its response to different neurotransmitter signals, doing so would be a major research undertaking, involving a significant amount of unpredictable experimentation with no guidance from Applicant's disclosure. This is considered to be an undue experimental burden.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance from the specification, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of all GABA modulation-responsive disorders.

Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating certain disorders, does not reasonably provide enablement for preventing those same disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. "Prevention" as discussed herein is interpreted to mean the complete blocking of all symptoms or effects of a disorder for an indefinite period of time.

Nature of the invention: The claimed invention is drawn to a therapeutic method for treatment or prevention of a disorder.

The state of the prior art: Certain GABA agonists are known in the art to be useful as anesthetics, sedatives, and antiepileptics. They are not known to be useful as preventative agents in the sense being used herein. In general, prevention of any disorder in the sense being used herein is not a recognized clinical outcome in the art, as no treatment is perfectly effective.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Prevention of a disease is not the same as treatment of said disease. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms? For example, will a metastatic cancer eventually adapt to overcome treatments directed to preventing it from metastasizing into the bone? Or will

a case of osteoporosis or rheumatoid arthritis ultimately progress to a point where symptoms develop regardless of which therapy is administered.

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many therapies which are suitable for short-term relief of symptoms are not suitable for lifelong prevention of disease. For example, antibiotics, chemotherapeutics, and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The Breadth of the claims: In the absence of an explicit definition in Applicant's specification, the claims are given their broadest reasonable interpretation. See MPEP 2111. Merriam-Webster's Collegiate Dictionary (reference included with PTO-892) defines "prevent" as meaning, "to deprive of power or hope of acting or succeeding," or "to keep from happening or existing." This definition is taken as representing the ordinary usage of the term "preventative". In order to deprive something of power or hope of acting or succeeding, the preventative agent must be completely effective. "Prevention" as recited in the instant claims, is interpreted to mean the complete and total blocking of all symptoms of a disorder for an indefinite period of time. Merely slowing the onset of disease or making the disease less likely would still leave it with "power or hope of acting or succeeding," and thus not qualify as prevention.

The amount of direction or guidance presented: No guidance is given in the specification suggesting any reason to believe that the claimed compounds are uniquely useful as preventative agents.

The presence or absence of working examples: No working examples are given of any therapeutic methods whatsoever.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of disease. See MPEP 2164.

The quantity of experimentation necessary: As mentioned above, the short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness for prevention of disease. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy. In particular, one skilled in the art, in order to practice the invention for prevention of disease, would need to know whether the preventative effect remains potent over the long term.

In order to answer these questions in the absence of any existing data, one skilled in the art, in order to practice the invention, would undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or monkeys, or a human clinical trial. Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional

burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Administering the claimed compounds for a period of years to a suitable subject population is an undue amount of experimentation needed in order to practice the full range of the claimed invention. As prevention in the full sense is an extremely high bar for any clinical outcome, there is no reason to believe that the therapy would be successful, and any actual success would be a surprising and unpredictable result.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the nature of the invention, Applicants fail to provide information sufficient to practice the claimed invention for the prevention of GABA-modulation-responsive disorders.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Teuber '00. (PCT international publication WO00/78728, reference included with PTO-1449, equivalent to US patent 6649609) Teuber '00. discloses a range of compounds including the compounds of claim 1. (pp. 3-6, wherein R^2 is alkyl, hydroxyalkyl, alkoxyalkyl, or alkyl-N-R^3R^4, and R'' is "heterocycle" representing pyrrolidin-1-yl, piperazin-1-yl, imidazoly-1-yl, or pyridine-4-yl (see p. 11, lines 15-19) substituted with hydroxyalkyl or alkoxyalkyl) When the heterocycle is piperazine, the compound anticipates claim 2, and when the heterocycle is piperidine the compound anticipates claim 3. These compounds are disclosed as pharmaceutical compositions together with at least one pharmaceutically acceptable carrier, excipient, or diluent, and are useful in methods of treating disorders responsive to modulation of the GABA receptor complex. (p. 6, lines 7-21) They are also useful as anesthetics, pre-anesthetics, sedatives, muscle relaxants, and anticonvulsants. (p. 2, lines 30-33) Therefore the claimed invention is anticipated by Teuber '00.

Claims 1, 3, 4, 7 and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Teuber '98. (PCT international publication WO98/17651, reference included with PTO-1449) Teuber '98. discloses a range of compounds including the compounds of claim 1. (pp. 6-10, wherein R^1 is CO_2R^2, R^2 is alkyl, alkenyl, or alkynyl, R^{11} is a 5 or 6 membered heterocyclic ring (see p. 8, lines 15-30) substituted with alkylcarbonylalkyl, alkenyl, or alkynyl) These compounds are disclosed as pharmaceutical compositions (p. 20, lines 18-24) together with at least one

pharmaceutically acceptable carrier, excipient, or diluent, and are useful in methods of treating disorders responsive to modulation of the GABA receptor complex, for example as muscle relaxants. (p. 25, lines 15-24) Therefore the claimed invention is anticipated by Teuber '98.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Teuber '00. (PCT international publication WO00/78728, reference included with PTO-1449, equivalent to US patent 6649609) The disclosure of Teuber '00 is discussed above. Additionally, on pp. 16-17 Teuber '00 discloses a number of specific embodiments having structures similar to those of instant claim 8, for example 2-Hydroxyethyl 1-(3-(4-(2-hydroxyethyl)-l-piperazinyl)-phenyl)- benzimidazole-5-carboxylate. (p. 16, lines 38-39) Teuber '00 does not specifically exemplify the compounds recited in instant claim 8.

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce the compounds of claim 8. One of ordinary skill in the art would have been motivated o produce various embodiments of the general formula of Teuber '00 and to evaluate them for their usefulness in the claimed invention. Because these compounds fall within the limits of the general formula disclosed by Teuber '00, and

because they are similar in structure to the specific embodiments disclosed therein, it would have been obvious to produce and evaluate them.

Therefore the invention taken as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6, and 9-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7, and 10-12 of U.S. Patent No. 6649609. (Cited in PTO-892, herein referred to as '609) Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-7 and 9-11 of '609 anticipate the claimed invention. Claims 1 and 7 of '609 disclose a formula that anticipates the instant claims when R^2 of claim 1 of '609 is hydroxyalkyl or

alkoxyalkyl, o is 0, Y is NR^{11}, and R^{11} is hydroxyalkyl or alkoxyalkyl. When X is N, '609 anticipates instant claim 2 and when X is CH, it anticipates instant claim 3. Claims 10-12 of '609 claim the same compositions and methods s instant claims 9-11. Thus the claimed invention is anticipated by claims 1, 7, and 10-12 of '609.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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